

# Clinical and Pathologic Characteristics of Myocarditis as a Cause of Sudden Death

Lena Avedissian, Jennifer A. McNear, David A. Appel, Laudino M. Castillo-Rojas, J. Edwin Atwood, Lisa A. Pearse, Robert N. Potter, Allen P. Burke, Ladd Tremaine, Philip J. Gentlesk, Eric A. Shry, S. Scott Reich, Robert E. Eckart

Department of Defense Cardiovascular Death Registry Group  
San Antonio, TX and Washington, DC



Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE <b>2008</b>		2. REPORT TYPE		3. DATES COVERED <b>00-00-2008 to 00-00-2008</b>	
4. TITLE AND SUBTITLE <b>Clinical and Pathologic Characteristics of Myocarditis as a Cause of Sudden Death</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>Department of Defense Cardiovascular Death Registry Group, Walter Reed Army Medical Center, Washington, DC</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT <b>Approved for public release; distribution unlimited</b>					
13. SUPPLEMENTARY NOTES <b>2008 Meeting of the American College of Physicians: Army and Air Force Chapters, held in Bethesda, MD, 19 November - 23 November 2008</b>					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT <b>Same as Report (SAR)</b>	18. NUMBER OF PAGES <b>17</b>	19a. NAME OF RESPONSIBLE PERSON
a. REPORT <b>unclassified</b>	b. ABSTRACT <b>unclassified</b>	c. THIS PAGE <b>unclassified</b>			

# Myocarditis

- ◆ Myocarditis as a cause of sudden death in the young population has widely variable incidence, ranging from 5 to 42%.
- ◆ Men may be more predisposed than women to develop myocarditis.
- ◆ Worse outcome in the younger population.
  - ◆ 162 subjects under the age 40 with myocarditis
  - ◆ Sudden death seen in 22% of those <30 years compared to only 11% in those between 30-40 years

# Etiologies

## Infectious myocarditis

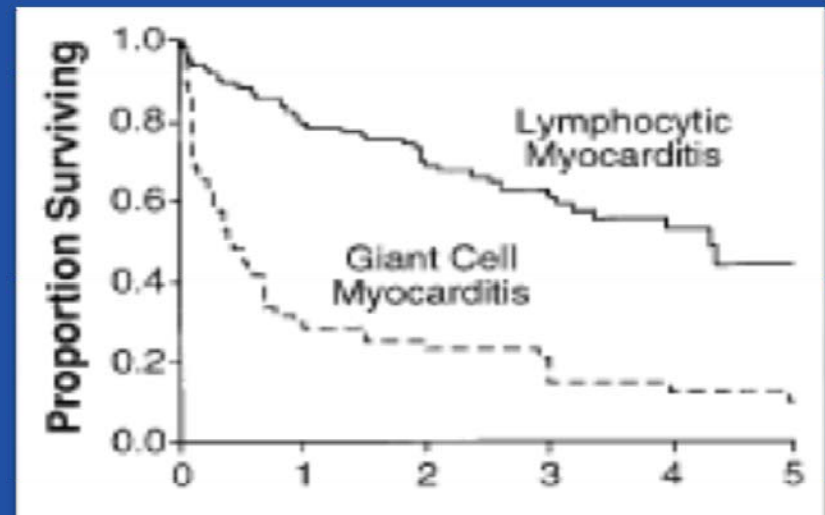
Enterovirus	Herpes virus	Rickettsial	Bacterial
Coxsackie A and B	Mumps	Fungal	Legionella
ECHO	Rubella	<i>Cryptococcus</i>	Clostridium
Influenza	Rubeola	Protozoan	Salmonella/Shigella
Polio	Hepatitis B and C	<i>Trypanosomiasis cruzi</i>	Spirochetal
Adenovirus	HIV	<i>Toxoplasmosis gondi</i>	<i>Borrelia burgdorferi</i>

## Noninfectious Myocarditis

Cardiotoxic drugs	Hypersensitivity drug reactions	
Catecholamines	Antibiotics	Diuretics
Doxorubicin	Ampicillin	HCTZ
Systemic illness	Tetracycline	Spironolactone
SLE	Sulfisoxazole	Others
Other collagen disease		Lithium
Sarcoidosis		Indomethecin

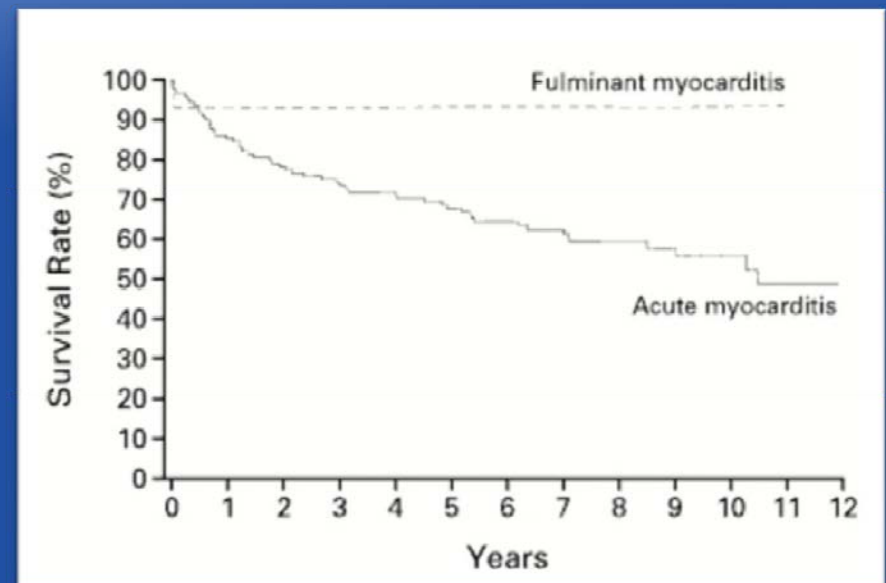
# Classifications of Myocarditis

- ◆ Active viral infection
- ◆ Postviral or lymphocytic myocarditis
- ◆ Other infectious etiologies
- ◆ Hypersensitivity myocarditis
- ◆ Giant cell myocarditis
  - ◆ Multinucleated giant cells
  - ◆ High mortality



# Clinical Presentation

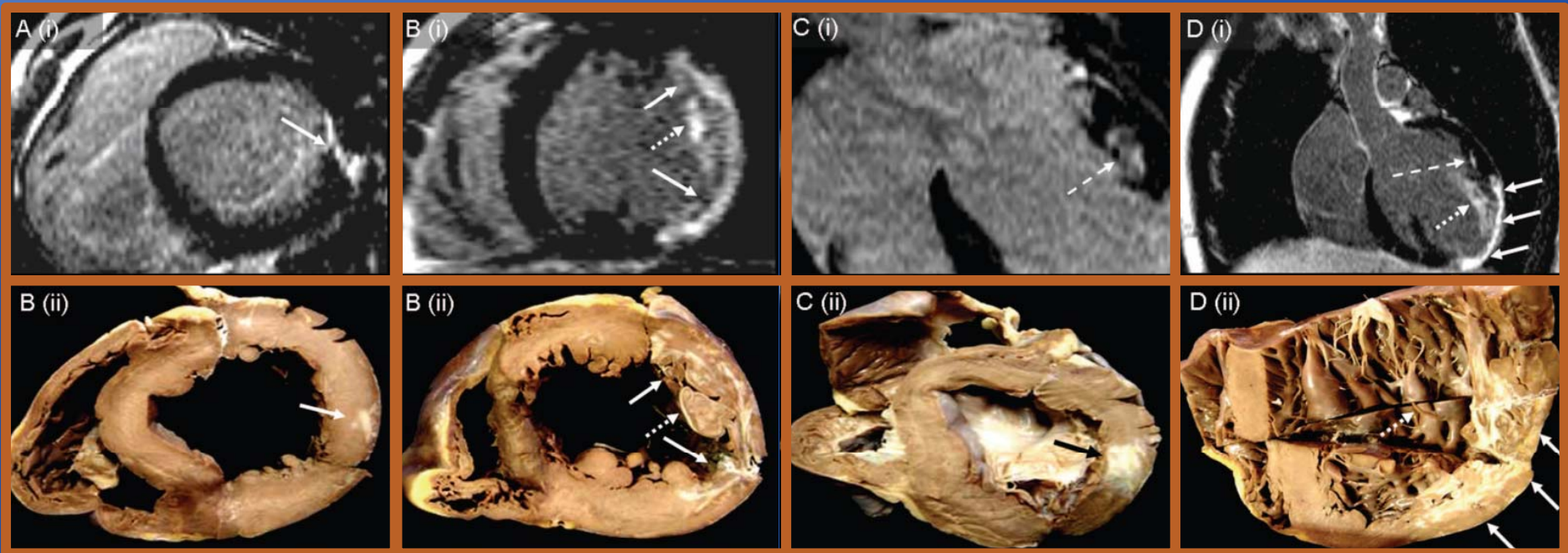
- ◆ Fulminant myocarditis
  - ◆ Acute critical illness
  - ◆ Distinct viral prodrome
  - ◆ Multiple foci of active myocarditis by histology
  - ◆ Favorable prognosis
- ◆ Acute myocarditis
  - ◆ Less distinct onset
  - ◆ Hemodynamically stable
- ◆ Chronic Myocarditis
  - ◆ Manifest with heart failure secondary to dilated cardiomyopathy



# Contributors to malignant cardiac arrhythmias in myocarditis

- ♦ Structural changes in the region of the injured myocardium, during both active myocarditis and healing (deleterious ventricular remodeling).
- ♦ Inflammatory process in the cardiac myocytes and interstitium can lead to fluctuations in the membrane potential.
- ♦ Activated neutrophils have been associated with generation of early after depolarization

# Fibrosis and scarring as substrate for both automaticity and reentry



# Study Design

- ◆ Review of non-traumatic sudden death within the Department of Defense with an available clinical record or autopsy for adjudication as to the cause of death.
- ◆ Statistical measures
  - ◆ Categorical variables were compared using the  $\chi^2$  test or the Fisher exact test and the Student's *t*-test was used to compare normally distributed continuous variables.
  - ◆ Differences considered statistically significant if  $p < 0.05$ .
  - ◆ JMP Professional (SAS Institute Inc., Cary, NC).
- ◆ Sponsored by the Air Force Medical Research Program (AF/SGRS).

# Defining the Cohort

- ◆ 902 non-traumatic suspected cardiac deaths
  - ◆ 1998 to 2008
  - ◆ Records available for review in which adjudicated cause of death was of cardiac etiology
- ◆ Identified 30 subjects with death due to myocarditis. Used 187 subjects with structurally normal heart as control group.

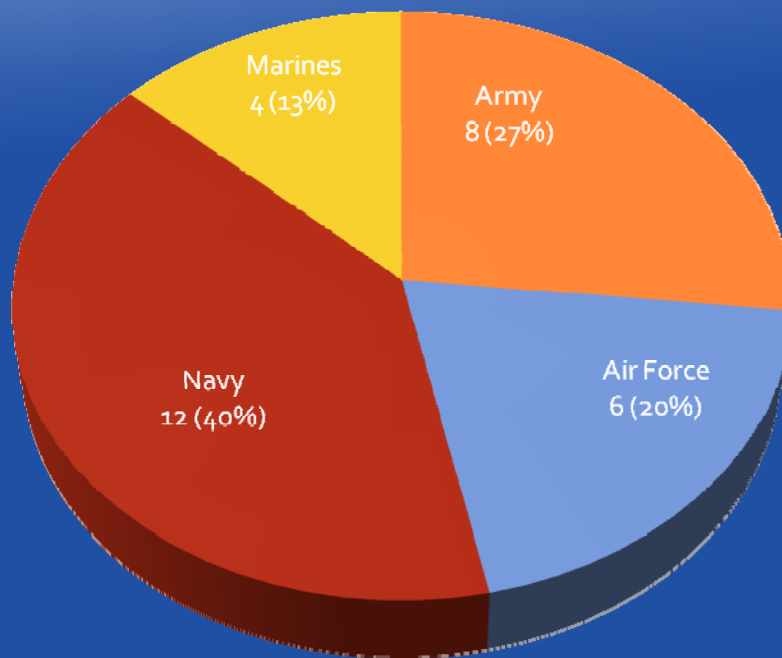
# Results

	Myocarditis n=30	Idiopathic SCD n=187	p-value
Age, years	32±10	32±11	0.940
Gender, % male	26 (86.7%)	174 (93.1%)	0.265
Prodromal symptoms	16/23 (69.6%)	48/99 (48.5%)	0.104
Fever, headache, URI symptoms	13/23 (56.5%)	0/99 (0.0%)	<0.001
Out of hospital death	5 (16.7%)	55(29.4%)	0.219

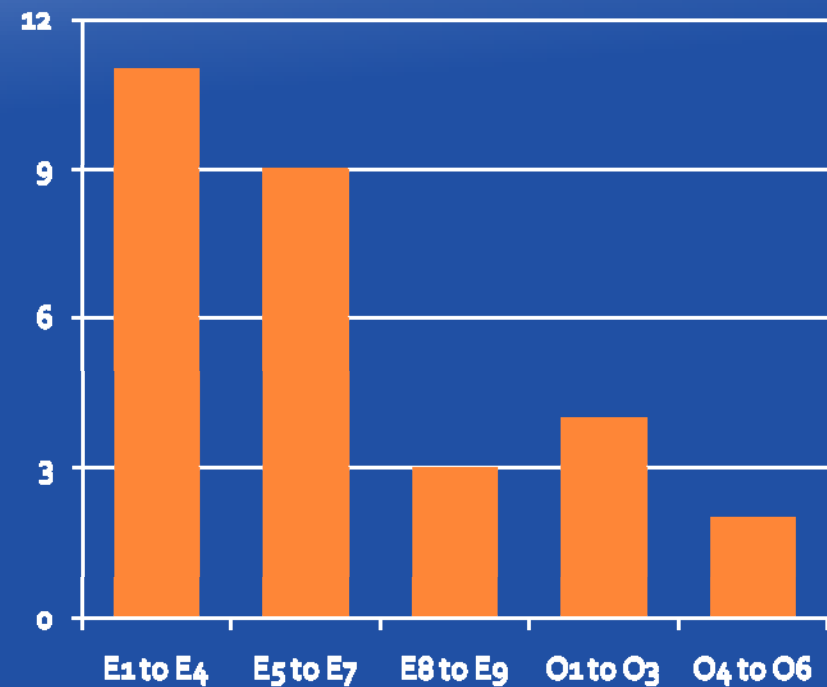
# Baseline Characteristics

Military specific findings for those with death due to myocarditis

**Branch**



**Column2**



Not shown is the 1 Warrant Officer

# Results

	Myocarditis n=30	Idiopathic SCD n=187	p-value
Myocardial measurements			
Cardiac mass, gms	451±88	395±72	<0.001
LV thickness, cm	1.6±0.4	1.5±0.3	0.033
RV thickness, cm	0.5±0.2	0.4±0.2	0.457
Valve circumference			
TV annulus, cm	13.7±2.0	12.7±1.7	0.158
PV annulus, cm	8.0±1.9	7.1±1.0	0.092
MV annulus, cm	11.1±1.0	10.7±1.1	0.385
AV annulus, cm	7.2±0.7	6.8±0.8	0.213
Histologic findings			
Fibrosis	11 (36.7%)	34 (18.2%)	0.038
Necrosis	13 (43.3%)	5 (2.7%)	<0.001
Disarray	2 (6.7%)	5 (2.7%)	0.250

# Ventricular specification

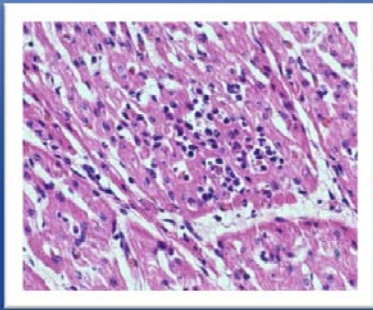
Isolated Right Ventricle  
Involvement  
31.3%

Isolated Left Ventricle  
Involvement  
25.0%

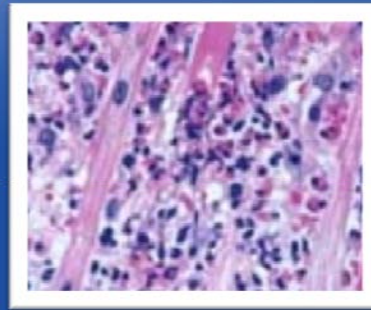


Bi-ventricle  
Involvement  
43.8%

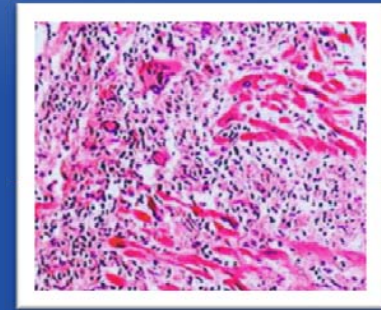
# Findings on Examination



Lymphocytic  
81.8%



Eosinophilic  
4.5%



Giant Cell  
9.1%

Findings on gross examination to suggest myocarditis were noted in 85.7% of cases.

# Conclusion

# Clinical and Pathologic Characteristics of Myocarditis as a Cause of Sudden Death

Lena Avedissian, Jennifer A. McNear, David A. Appel, Laudino M. Castillo-Rojas, J. Edwin Atwood, Lisa A. Pearse, Robert N. Potter, Allen P. Burke, Ladd Tremaine, Philip J. Gentlesk, Eric A. Shry, S. Scott Reich, Robert E. Eckart

Department of Defense Cardiovascular Death Registry Group  
San Antonio, TX and Washington, DC



# Defining Myocarditis

## ◆ Dallas Classification (1987)

- ◆ Myocarditis: Myocardial necrosis, degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrate with or without fibrosis.
- ◆ Borderline myocarditis: Inflammatory infiltrate too sparse or myocyte damage not apparent.
- ◆ No myocarditis:

## ◆ WHO Marburg Criteria (1996)

- ◆ Acute (active) myocarditis: A clear-cut infiltrate (diffuse, focal or confluent) of  $>14$  leukocytes/mm<sup>2</sup> (preferably activated T-cells). The amount of the infiltrate should be quantitated by immunohistochemistry. Necrosis or degeneration are compulsory, fibrosis may be absent or present and should be graded.
- ◆ Chronic myocarditis: An infiltrate of  $>14$  leukocytes/mm<sup>2</sup> (diffuse, focal or confluent, preferably activated T-cells). Quantification should be made by immunohistochemistry. Necrosis or degeneration are usually not evident, fibrosis may be absent or present and should be graded.
- ◆ No myocarditis: No infiltrating cells or  $<14$  leukocytes/mm<sup>2</sup>.